An Exact 3D Monte Carlo Simulation of Signaling Events in the Cardiac Myocyte

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In recent years, there has been much interest in intracellular signaling processes that take place in subcellular microdomains. These local signaling events have been shown to play an essential role in regulating cell function. In such subspaces, the number of molecules can be small enough to render the notion of concentration invalid. Here we propose using the exact 3D Monte Carlo approach (using MCell software) to better describe signaling events. With the use of this approach, we are able to track the positions of individual molecules on different spatial and temporal scales. By specifying relevant diffusion constants, reaction kinetics, geometry, participating molecules and an appropriate reaction time step, we can then predict the influence of changes in the physical environment on signaling processes. We use the cardiac myocyte as a test case for this simulation method.
In the cardiac myocyte, Ca^{2+} influx via voltage-gated L-type Ca^{2+} channels (LCCs) triggers Ca^{2+} release from ryanodine receptors (RyRs). This mechanism called Ca^{2+}-induced Ca^{2+} release (CICR) operates in the dyadic subspace where LCCs are closely apposed to RyRs across an estimated 10-20 nm cleft. In this minute compartment between the sarcolemmal membrane and sarcoplasmic reticulum, localized Ca^{2+} signaling events control excitation-contraction (EC) coupling in a tightly regulated manner. However, this control can be disrupted in the presence of β-adrenergic stimulation or changes to cardiac myocyte morphology, potentially leading to defective heart function.

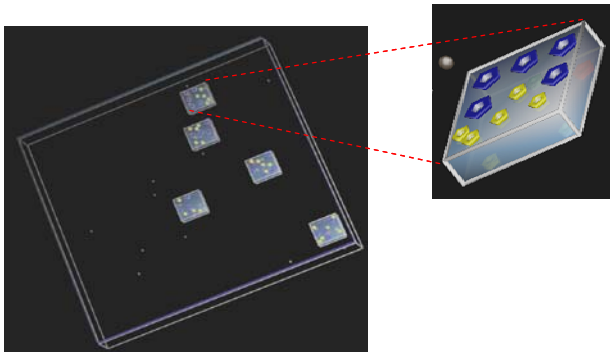

Figure illustrates a 3D visualization of the 12 nm × 500 nm × 500 nm diadic subspace. Shaded regions (see inset) show localization of multi-molecular complexes. Signaling ions are shown freely diffusing in the system.

In the model presented, we study stochastic events in Ca^{2+} signaling, paying attention to the localization of Ca^{2+} release channels and other proteins that modulate EC coupling such as PKA. We consider events in a diadic subspace volume of 12 nm × 500 nm × 500 nm, where signaling molecules are organized into multi-molecular complexes. The trigger of Ca^{2+} sparks by CICR requires a precise alignment of LCCs and RyRs on their respective membranes. Disruption of healthy cleft geometry can interfere with the tight local control between these calcium channels, leading to pathological alterations in Ca^{2+} signaling. Our study has revealed how reaction specificity in the modeled subspace is regulated by geometry as well as the organization of signaling molecules into functional complexes. We also predict the influence of β-adrenergic stimulation on Ca^{2+}-regulated events. Detailed understanding of how the above factors implicate Ca^{2+} signaling can provide the basis for therapies of dysfunctions like heart failure and arrhythmia.